Claim 14 is objected to under 37 CFR 1.75(c), as being of improper dependent form failing to further limit the subject matter of the previous claim. After the election of species, Claims 12 and 14 become identical. Cancellation of one claim is required.

Applicant agrees with Examiner that Claim 14 is identical to Claim 12. Applicant has cancelled Claim 14.

Rejections of Claims 1-3, 5, 7-10, and 41-43 under 35 U.S.C. § 112

Claims 1-3, 5, 7-10, 12, 14, and 41-43 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention. The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art in the breadths of the claims. *Ex Parte Formen*, (230 USPQ 546) Bd Pat. App. & Int. 1986)); *In re Wands*, 858 F. 2d 731,8 USPQ 2d 1400(Fed. Cir. 1988). The Examiner states that Claims 1-3, 5, and 7 are drawn to methods enhancing the interaction of an artery-specific molecule with a vein-specific molecule and that the specification describes an artery specific molecule EphrinB2 that interacts with a vein specific molecule EphB4 but no guidance is presented for the identification of factors enhancing the interaction. Applicant respectfully disagrees, Applicant cites numerous approaches to screening agents for their selective effects on arteries and veins. For example, high-throughput screening (page 20, line 6). Additionally, Applicant discloses detailed methods to identify factors which enhance this interaction, for example (page 20, line 25 through page 21, line 3), which states that immortalized cell lines of arterial or venous origin can be used to screen libraries of compounds to identify drugs with artery- or vein-specific angiogenic or antiangiogenic effects. In one embodiment, an assay can be carried out to screen for drugs that specifically enhance binding of an Ephrin ligand to its Eph receptor such as binding of EphrinB2 to the Eph B4 receptor, or vice versa, by enhancing binding of labeled ligand or Fc-fusion proteins to immortalized cells (page 30, line 15-30). Additionally, Applicant provides guidance (page 22, line 9-13) as to what parameters encompass "enhancing". For example, the specification states that if the extent to which interaction at cell specific molecules occurs is greater in the presence of the drug then in the absence of the drug, the drug is one which

enhances interaction of the arterial endothelial cell-specific molecule with the venous endothelial cell-specific molecule. Therefore, the Applicant has provided sufficient guidance to one skilled in the art, for the identification of factors enhancing interaction between an artery-specific molecule with a vein-specific molecule under 35 U.S.C. § 112.

The Examiner states (page 3-4) in absence of such guidance, given the unpredictability of identifying enhancing factors, it would require undue experimentation by one of skill in the art to make and use the invention as described in the instant claims. Respectfully, Applicant refers Examiner to MPEP §2164.01 which states that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culturer Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d. 1104, 227 USPQ 428 (Fed. Cir. 1985). Assays disclosed utilize methods know to those of skill in the art and thus would not require undue experimentation, for example, high-throughput screening, labeling of ligands or receptors, and generation of transgenic mice. Applicant's invention, combined with state of the art, and guidance as given above, clearly enable the identification enhancing factors. Applicant requests the rejection of Claims 1-3, 5, 7 under 35 U.S.C. § 112 be withdrawn.

The Examiner also states while the specification describes a molecule, EphrinB2, that is present on the surface of arterial endothelial cells but not venous endothelial cells, this molecule is known to be in other tissues types (Pasquale, Curr. Opin. Cell. Biol., Vol. 9, pages 608-615, 1997) and that it would therefore not be predictable that agents directed against EphrinB2 would target specifically to arteries; other tissues would also be affected. Respectfully, Applicant disagrees with the Examiner's interpretation. The fact that EphrinB2 is expressed in non-vascular tissues is irrelevant. Applicant has found that administration of macromolecular compounds via the circulation would prevent their access to other, non-vascular tissues expressing Ephrin B2. Thus, no deleterious side effects in other tissues would be predicted. Further, Applicant disagrees with the Examiner that it is not predictable that agents targeted against EphrinB2 would not specifically be targeted to the arteries. Applicant discloses several examples in the specification, for example, the DNA construct used to make the transgenic EphrinB2 knock out mouse targeted properly to arteries, as described in Example 1 (page 35, line 2-6) of the specification. It is art standard that agents made against a molecule specifically associate. Applicant discloses one embodiment of the invention, as described in the specification

(page 28, line 4-25), using a complex comprising a drug and a macromolecular component which is directed against an artery-specific molecule, to target a drug to arteries. Accordingly, Claims 8-10, 12 and 14 are enabled and Applicant requests that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

The Examiner further states that while it might be expected that the extracellular region of EphB4 would bind to EphrinB2 and stimulate tyrosine phosphorylation of EphrinB2 and signal transduction (Bruckner et al. Science, Vol. 275, pages 1640-43, 1997), it is by no means clear that polypeptides comprising this extracellular domain would have this function and that there is no indication of what additions to the extracellular region of EphB4 would be tolerated and what additions would not be tolerated. Applicant respectfully suggests that the Examiner has misinterpreted claims 41-43. Applicant suggests the use of soluble polypeptides comprising the extracellular domain of artery- or vein-specific proteins (page 30 line 15-30). Applicant discloses a method for altering (inhibiting or stimulating) blood vessel development by administering a soluble polypeptide comprising the extracellular domain of an artery- or vein-specific cell-surface protein. The use of extracellular domains of cell surface proteins (i.e. receptors and ligands) to alter biological function is well documented in the art. For example, Wang and Anderson (Neuron Vol. 18, pages 383-396, 1997) demonstrate that addition of soluble extracellular domains of Eph family ligands, Lerk2 and HtkL, alter neural crest cell migration and axonal guidance. Additionally, a soluble form of the Eph family ligand, B61, has been shown to be an angiogenic factor *in vivo* (Pandey et al., Science, Vol. 268, pages 567-569). Furthermore, there are many examples of polypeptides comprising the extracellular domain of growth factor receptors whose interactions result in altered biological function. For example, a soluble form of Fibroblast Growth Factor Receptor 2b perturbed multi-organ induction and patterning (Celli et al. Embo J., Vol. 17, 1642-1655, 1998).

The Examiner also states the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of what alterations can be made is extremely complex and well outside the realm of routine experimentation. Although the prediction of the three-dimensional structure of a molecule is complex, the prediction of protein domains such as extracellular, transmembrane and cytosolic are not. The structural properties of most proteins can be deduced from their amino acid sequence via a computer search for homologs. Additionally, the structural properties of Eph and Ephrin family proteins are detailed in the specification (page 6, lines 15-20, page 9, line 22 through page 10, line 11). This

information is obtainable by one of skill in the art. Furthermore, it is known in the art to determine empirically the function of said structural components. One advantage of the Applicant's invention is the ability to identify artery- or vein-specific cells and to assess the effect of the soluble polypeptides on biological function. Therefore, no undue amount of experimentation is required. Thus, Applicant respectfully requests that the rejection of Claims 41-43 under 35 U.S.C. 112, first paragraph be withdrawn.

The Examiner states that Claim 41 requires the existence of a vein-specific molecule that interacts with an artery-specific molecule and that while artery-specific responses are known and differences in cell-surface receptors between arteries and veins have been suggested (Simonet et al., Euro. J. Pharm., Vol. 216, pages 135-137, 1992), there are no examples of artery and vein-specific molecules other than EphrinB2 and EphB4 described in the instant specification or the available art of record. The Examiner concludes that it is therefore not predictable that other such molecules even exist. Respectfully, Applicant disagrees. Applicant argues that other artery or vein-specific molecules have been predicted in the art. For example, Wang et al. (Cell, Vol. 93, page 750) states that Applicant's results indicate that the physiological and pathological distinctions between mature arteries and veins are not simply due to differences in their anatomy, oxygenation, or blood pressure, but rather are genetically determined and thus implies that arteries and veins are likely to differ in their expression of many other genes as well. Therefore, one of skill in the art would reasonably predict that there are many molecules which are artery- or vein-specific to be identified.

The Examiner further states that Ephrins and their receptors are widely distributed and understood primarily in their role in neural development (Pasquale, Curr. Opin. Cell. Biol. Vol. 9, pages 608-615, 1997) and that their function in arterial and venous determination is an emerging field of research and no other examples of signaling pairs are described either in the instant specification or the available art of record and that since the instant example was identified by generating a transgenic mouse, it would not be predictable that similar pairs could be identified, nor a similar approach be taken without undue experimentation by one skilled in the art. Respectfully, Applicant disagrees. Even if no other artery or vein-specific pairs are cited other than EphrinB2/EphB4, the prediction in art of record is that they do exist and hence, could be identified. For example, another artery-specific cell surface molecule, Dll-4, has been identified (Shutter *et* al., *Genes and Dev.*, Vol. 14, pages 1313-1318). Further, Applicant discloses several methods to identify additional artery- and vein-specific molecules. For

example, isolation of artery- or vein-specific cDNAs through the use of disclosed antibodies (page 3, line 28 through page 4, line 1), generating cells which produce an artery- or vein-specific fusion protein with a green fluorescent indicator protein portion or a blue fluorescent indicator protein portion and separating from non-fluorescent cells by a cell sorter (page 17, line 11 through 25). The Examiner also states that one skilled in the art would require further guidance, in the form of less technologically complex approaches with a more predictable outcome in order to use the invention as claimed. Respectfully, Applicant refers examiner to MPEP §2164.01, cited earlier herein, which states that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. Applicant's specification provides ample guidance which would enable one of skill in the art to practice the invention. Furthermore, Applicant's specification defines the essential parameters to identify the desired products. Therefore, using the methods of the instant invention, the suggestion that its is likely that other artery and vein-specific exist, and the parameters to identify such molecules as disclosed in the specification, the amount of experimentation is not undue. In summary, in light of the arguments above, Applicant believes Claims 41-43 meet the requirements of 35 U.S.C. §112, first paragraph and are therefore allowable. Applicant requests that the rejection of Claims 41-43 under 35 U.S.C. §112, first paragraph be withdrawn.

Rejection of Claims 1-3, 5, and 7 under 35 U.S.C. §112, second paragraph.

The Examiner states that "interaction" is not defined in the specification. In the absence of an explicit definition, the parameters defining an "interaction" would not be evident to one skill in the art. One of skill in the art would therefore not be able to identify factors affecting said interaction. Respectfully, Applicant disagrees with the assertion that the "parameters" would not be evident to one of skill in the art. Applicant's specification (page 21, line 25 through page 23, line 14) discloses several examples that detail precisely parameters sufficient to assess interactions between artery and vein-specific molecules. In the Examples, the molecule specific to one cell type is fixed to a solid support while the molecule specific to the other cell type is found free in a solution that allows for the interaction of the specific molecules. In further steps of the assay, the extent to which a cell-specific interaction is determined, in the presence of a drug, and in a separate test (control), in the absence of said drug. The extent to which the interaction of the cell-specific molecules occurs in the presence and in the absence of a drug to be assessed is compared. If the extent to which interaction of cell-specific molecules occurs is less in the presence of a drug than in the absence of the same drug, said drug is one which inhibits

interaction of the arterial endothelial cell-specific molecule with the venous endothelial cell-specific molecule. If the extent to which the interaction of a cell-specific molecules occurs is greater in the presence of a drug than the absence of said drug, said drug is one which enhances interaction of the arterial endothelial cell-specific molecule with the venous endothelial cell-specific molecule. Therefore, the Applicant has clearly defined the parameters of interaction between cell-specific molecules and several methods to assess the proposed interaction in their specification. Hence, given the extensive guidance in the specification, the interaction of an artery- and vein-specific factors would be evident to one of skill in the art. Thus, Claims 1-3, 5, and 7 are not indefinite under 35 U.S.C. §112, second paragraph and the Applicant requests that the rejection be withdrawn.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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